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Effects of Long Term Sertraline Treatment and Depression on Coronary Artery Atherosclerosis in Premenopausal Female Primates

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Abstract

Objectives—Major depressive disorder and coronary heart disease (CHD) often co-occur in the same individuals. Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for depression and other disorders, but their effects on CHD risk remain unclear. We determined the effects of a SSRI on coronary artery atherosclerosis (CAA) in an established nonhuman primate model used to clarify the association between depression and CAA.

Methods—42 adult female cynomolgus macaques consuming a Western diet were characterized during an 18-month pretreatment phase, and assigned to SSRI (sertraline HCl 20 mg/kg, po, once/day) or Placebo balanced on pretreatment depression, body weight (BW), and iliac artery atherosclerosis extent measured via biopsy. After 18 months CAA extent was measured using histomorphometry.

Results—Before and during treatment depressed monkeys had lower BW, body mass index (BMI), and plasma high density lipoprotein cholesterol, and higher heart rates during the pretreatment ($p < 0.01$) but not the treatment phase ($p = 0.17$). There were no pretreatment differences between the sertraline and placebo groups. Sertraline reduced anxious behavior but had no effect on BW, BMI, heart rate, plasma lipids, or depression. CAA, analyzed by a 2 (Depressed, Nondepressed) $\times$ 2 (Placebo, Sertraline) $\times$ 3 (coronary arteries) analysis of covariance adjusted for pretreatment iliac atherosclerosis, was greater in depressed than nondepressed monkeys ($p < 0.036$), and in sertraline than placebo-treated monkeys ($p = 0.040$). The observed CAA extent in depressed monkeys treated with sertraline was 4.9 times higher than in untreated depressed monkeys, and 6.5 times higher than in non-depressed monkeys, on average.

Conclusions—Depressed animals develop more CAA, and that longterm treatment with sertraline promotes CAA.

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Keywords

Selective serotonin reuptake inhibitor; coronary artery atherosclerosis; depression; nonhuman primates; females; CHD

Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality of women in the US--exceeding that of all cancers combined. CHD in women is understudied, and less well understood than in men (1). Coronary artery atherosclerosis (CAA) and its sequelae are frequent causes of CHD. The premenopausal life stage is important in determining the extent of postmenopausal CAA and CHD risk because the extent of premenopausal CAA sets the starting point and trajectory for coronary artery plaque progression in the postmenopause (2).

Depressive disorders are twice as likely in women as men (3). The lifetime prevalence of depression in women is 20%, occurring most commonly in the reproductive years (4). Excluding suicide, major depression is associated with increased mortality, in part due to a high rate of co-morbidities (5–7). The co-morbidity of depression and CHD is particularly marked (8). Several studies demonstrate graded relative risk of CHD with depression, suggesting that milder forms of depression in addition to major depressive disorder may be clinically relevant (9–11). Since CHD is the leading cause of death of women, depression may be particularly important to the cardiovascular health of women (12).

Antidepressants are the most frequently used medication by 18–44 year olds, and the third most commonly prescribed drug taken by Americans of all ages. Women are 2.5 times more likely than men to take antidepressants, and 23% of women aged 40–59 take antidepressants. Among Americans taking antidepressant medications, 60% have taken these drugs for 2 years or longer, and 14 % for 10 years or more. Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants in the United States (National Health and Nutrition Examination (NHANES) (13) Survey 2005–2008. In addition to depression, SSRIs are prescribed for a number of other disorders including obsessive-compulsive disorder (14), bulimia and binge eating (15), agitation and aggression in dementia and other central nervous system degenerative diseases (16), fibromyalgia, osteoarthritis, and diabetic neuropathy pain (17), hot flashes (18), stroke recovery (19), and premature ejaculation (20). Due to their widespread use, knowledge of the multi-system effects of these medications is important for the public health.

There has been much discussion over the last several years about whether SSRIs are safe for treating depression in CHD patients (21, 22). Some have gone so far as to recommend SSRIs to inhibit atherosclerosis progression (23). These recommendations stem from evidence of perturbed cardiovascular risk factors in depression including arrhythmias, platelet reactivity, proinflammatory processes, hypothalamic-pituitary-adrenal (HPA) function, and low high-density lipoprotein cholesterol (HDL) concentrations in women (9, 24–28). Of these risk factors, the available evidence suggests that SSRIs have inhibitory effects on platelet reactivity (29) and inflammatory processes (30, 31) although evidence that these affects

have cardiovascular significance is scarce. Conversely, SSRIs also have been observed to have adverse effects on CHD risk factors including increasing body weight (BW), body mass index (BMI), waist circumference, fasting glucose, total plasma cholesterol (TPC), low density lipoprotein cholesterol, and triglyceride concentrations (32–34), all factors that may be affected by food consumption. It is notable that many disorders for which SSRIs are commonly prescribed, such as depression, also may affect food consumption. Since all the SSRI-CHD risk factor studies assessed patient populations, the effects of SSRIs on these CHD risk factors are confounded by the disorder for which they were prescribed.

There are no experimental investigations of the effects of SSRIs on CAA extent and severity, and few long term clinical studies of the effect of SSRI use on CHD morbidity and mortality. SADHART (Sertraline AntiDepressant Heart Attack Trial) demonstrated that sertraline was relatively safe and efficacious in depressed patients with ischemic heart disease but was underpowered to detect a mortality difference between sertraline and placebo. Secondary analyses of the ENRICHD (ENhancing Recovery in Coronary Heart Disease) trial suggested that SSRIs in myocardial infarction patients might reduce subsequent morbidity and mortality but the trial was not designed to detect these relationships (35, 36). More recently, Rieckmann et al observed increased cardiovascular morbidity and mortality in patients using SSRIs compared to non-SSRIs or no antidepressant, in a 42 month follow up study of CHD patients (37).

In contrast, several studies suggest that SSRI use may increase the risk of ischemic stroke. Since ischemic stroke is due to cerebrovascular atherosclerosis and its sequelae, it may indicate atherosclerosis in other arterial beds. A recent meta-analysis of these studies suggests that the use of SSRIs is associated with an odds ratio of 1.48 (CI=1.08, 2.02) for ischemic stroke (38). Since these were observational studies, the effects of SSRIs may be confounded by the disorder for which they were prescribed. For this reason, a subgroup meta-analysis was done of the studies in which potential confounding due to depression was controlled by adjusting for severity of depression and/ or by exclusively selecting patients with depression. In this subgroup analysis, SSRIs still increased the risk of ischemic stroke. While these observations are suggestive, they do not address whether SSRIs affect the progression of atherosclerosis *per se*. However, there was a recent report of an association between increased carotid intimal-medial thickening, a powerful predictor of myocardial infarct risk (39), and SSRI treatment in a study of twins discordant for SSRI use (reported by Shah et al at the 2011 American College of Cardiology Scientific Sessions). In addition, among women with symptoms of myocardial ischemia, the use of antidepressant medication was associated with subsequent cardiovascular events (e.g. nonfatal myocardial infarction, stroke, congestive heart failure, unstable angina) (40).

Taken together, these observations of associations of worsened cardiovascular risk factors, increased ischemic stroke incidence, and carotid intimal-medial thickening with SSRI use suggest a need for better information concerning SSRI effects on the development and progression of atherosclerosis. As long term randomized clinical trials are unlikely due to cost and ethical considerations, preclinical investigations are needed. Here we used adult female cynomolgus monkeys (*Macaca fascicularis*) because they are among the best models of social stress, depression, and atherosclerosis pathogenesis. In response to the

consumption of a Western-like diet, these animals develop arterial plaques that are similar in location and composition to those of human beings (41).

Adult female cynomolgus monkeys are also an established model of the comorbidity of depression and CAA (25, 42, 43). Like people, monkeys may respond to the stress of low social status with depressive behavior accompanied by perturbations HPA, autonomic nervous system, lipid metabolism, ovarian, and neural serotonergic system function, all of which are associated with exacerbated CAA (25). Depressed female monkeys develop about four times more CAA than their nondepressed counterparts (43). Thus, this is an ideal model in which to study the effects of long term SSRI treatment on CAA and associated risk factors. Since SSRIs are prescribed for many disorders other than depression, both depressed and nondepressed monkeys were studied. We hypothesized that SSRI treatment would result in less CAA, and this affect would be most apparent in depressed monkeys as they develop the most CAA.

Methods and Materials

Subjects

Forty-five adult, reproductive-aged female cynomolgus monkeys were imported from Indonesia (Institut Pertanian Bogor, Bogor, Indonesia) and single cage quarantined for one month. Following quarantine, the monkeys were randomly assigned to social groups of $n=4-5$, in indoor pens ($3.05\text{m} \times 3.05\text{m} \times 3.05\text{m}$), in a climate controlled building, with 12/12 light/dark, and water *ad libitum*. All monkeys were fed a Western-like diet containing 44% of calories from fat and 0.29 mg/Cal cholesterol, comparable to a human consumption of 500 mg cholesterol/2000 calories, or 2 eggs per day (44). The monkeys were approximately 15.7 ± 0.3 years of age, estimated from dentition, which is approximately equivalent to a human age of 50–60 years. During the 3.5 year study, three animals died of causes unrelated to the experiment (2 from diarrheal disease and 1 from neoplasm) resulting in a final sample size of 42. All procedures involving primates were conducted in accordance with institutional, state, and federal laws for the use of nonhuman primates in laboratory settings and approved by the institutional animal care and use committee.

Experimental Design (Figure 1A)

The monkeys consumed the Western-like diet for an 18 month Pretreatment Phase during which depressive behavior was recorded. At the end of the 18 months, a portion of one iliac artery was removed surgically and the extent of atherosclerosis measured. All monkeys were trained to run out of their social group pens into a dosing cage and comply with an oral dosing regimen. Stratified randomization was used to assign the monkeys by social group to either placebo ($n=21$) or sertraline ($n=21$) treatment balanced on Pretreatment rate of depressive behavior, BW, and iliac artery atherosclerosis extent. Thus, all animals within a social group had the same treatment. Sertraline HCl (Zoloft®) was introduced gradually over a 4 week period until the final dose of 20 mg/kg was attained. Throughout the treatment phase sertraline was administered orally in vehicle daily at about 0800 hrs; the placebo group received vehicle alone.

Circulating Sertraline and Desmethylsertraline Concentrations

After the monkeys had been administered the 20 mg/kg dose for a week (week 5 of dosing) or placebo, they were sedated with 10–15 mg/kg ketamine HCl and blood samples were taken to measure circulating sertraline and desmethylsertraline as previously described (44). During placebo administration sertraline/ desmethylsertraline were undetectable. After 1 week at the 20 mg/kg dose, circulating concentrations of sertraline/ desmethylsertraline rose to average levels of 78 and 88 ng/ml, respectively (44), comparable to circulating levels observed in patients (45).

Cerebrospinal Fluid (CSF) Monoamine and Metabolite Determinations

Also, after the monkeys had been administered the 20 mg/kg dose for a week (week 5 of dosing) or placebo, CSF samples were taken for determination of central monoamine and metabolite concentrations. CSF was taken by inserting a 22-gauge needle percutaneously into the cisternal space while the animal was restrained in lateral recumbency. Approximately 1–1.5 cc of spinal fluid was obtained and frozen at -70°C until analysis. CSF 5-HIAA concentrations were determined using HPLC with electrochemical detection as previously described (43). Intra- and interassay coefficients of variation were $<10\%$. Compared to placebo, after 1 week of 20 mg/kg sertraline, CSF levels of 5-HIAA decreased 33% relative to the baseline levels. Thus, a clinically relevant oral dose of sertraline resulted in CSF metabolite changes similar to those observed in patients (46).

Behavior Observations

The definition of depressive behavior (Figure 1B) includes three components: 1) a slumped or collapsed body posture; 2) a relative lack of responsiveness to environmental stimuli to which other monkeys are attending; and 3) open eyes to distinguish this behavior from resting or sleeping (42). The frequency with which the monkeys were observed in the depressed posture was recorded for 10 minutes, twice/week, counterbalanced for time of day, for 12 months during the Pretreatment Phase, and 12 months during the Treatment Phase (an average of 33.3 hours/monkey total), using a focal animal technique that has been described in detail previously (43). Depressive behavior is easily recognizable; and inter-rater reliability, determined biannually, was $r = 0.92$ throughout the experiment. The average frequency/hour that the monkeys exhibited this behavior was calculated from these observations. Similar to previous studies, 23 monkeys (55%) displayed little or no depressive behavior (4 instances or less observed during the 18 month Pretreatment Phase) and were considered nondepressed in the analysis. The rate of self-directed behaviors including scratching and self-grooming was also recorded as a behavioral indicator of anxiety (47–51). Scratching was operationally defined as moving the fingertips repeatedly across the same skin area for a duration longer than one second, and self-grooming was defined as combing skin, hair, teeth or nails with hands.

Anthropometrics

BW and trunk length were measured at the end of the Pretreatment Phase, and 16 months after the onset of the Treatment Phase. BMI was estimated as the ratio of BW to the square of trunk length measured from the suprasternal notch to the pubic symphysis (kg/m^2) (52).

Plasma lipids/lipoproteins

After an 18–24 hour fast, blood samples were collected into EDTA tubes during the Pretreatment Phase at 4, 8, 12, and 16 months, and after 3, 10, and 17 months of treatment to determine fasting lipid/lipoprotein concentrations. TPC and HDLC concentrations were determined in the Wake Forest Comparative Medicine Clinical Chemistry and Endocrinology Laboratory using reagents (ACE cholesterol, ACE HDL-C, and ACE TG) and instrumentation (ACE ALERA autoanalyzer) from Alfa Wasserman Diagnostic Technologies (West Caldwell, NJ) (53). TPC and HDLC were standardized to calibrated controls from the Centers for Disease Control and Prevention, National Heart, Lung, and Blood Lipid Standardization Program. Intra- and inter-assay coefficients of variation were lower than 5% for all analyses.

Ovarian function

The monkeys were trained to present themselves for vaginal swabbing to detect menses and for femoral venipuncture for blood sample collection, three times a week for 1 year during the Pretreatment Phase and 1 year during the Treatment Phase. Circulating progesterone concentrations were determined by radioimmunoassay (Siemens/Diagnostic Products Corp., Los Angeles, CA). Progesterone concentrations in approximately 5 blood samples per luteal phase (~60 samples per monkey per year, ~2500 Pretreatment Phase and 2500 Treatment Phase samples), were used to estimate menstrual cycle quality. The maximal progesterone value in the luteal phase was used to represent the peak progesterone for that menstrual cycle. Peak progesterone concentrations >4 ng/ml suggest successful ovulation, <2 ng/ml suggest an anovulatory cycle, and values between 2 and 4 ng/ml are considered impaired (54). Mean peak progesterone concentrations, average cycle length, and the number of cycles were calculated for each female for analysis.

Heart Rate (HR)

Autonomic nervous system responsivity was assessed by recording HR via telemetry. Each monkey was outfitted with a nylon mesh protective jacket over a portable electrocardiogram telemetry unit as previously described (52). After a 24 hour recovery period, HRs were recorded for the next 24 hours, and average hourly HRs were calculated. HR was recorded at the end of the Pretreatment Phase and at the end of the Treatment Phase.

Iliac Artery Biopsy and Measurement of Atherosclerosis Extent

At the end of the Pretreatment Phase, the monkeys were anesthetized and a segment of the left common iliac artery was removed, opened longitudinally, divided into three congruent segments cut perpendicular to the long axis of the artery, and the central segment was laid flat on cardboard and immersion-fixed in 10% neutral buffered formalin. The fixed segment was embedded in paraffin, sectioned, stained, and the extent of atherosclerosis was measured as the area (in mm²) between the internal elastic lamina and the lumen.

Necropsy and Measurement of Coronary Artery Atherosclerosis

At necropsy, animals were anesthetized deeply with pentobarbital (60 mg/kg), the cardiovascular system was flushed with normal saline, and the heart removed and perfusion

fixed with 10% neutral buffered formalin under a pressure of 100 mm Hg. After fixation, five standard serial blocks, 3 mm in length, were taken from each of the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). Each of the 15 blocks was embedded in paraffin, and 5- μ m sections were cut and stained with Verhoeff-van Gieson's stain. Images of each section were captured digitally using a Nikon DS Fi1 camera mounted on an Olympus BH-2 microscope equipped with a mechanical stage. Morphometric measurements were made using Image-Pro Plus version 7.0 imaging software (Media Cybernetics Inc., Bethesda, MD). Plaque extent is expressed as the cross-sectional area (mm^2) of the area between the internal elastic lamina and the lumen (55,56).

Statistical Analysis

Log transformation was used to reduce skewness and heterogeneity of variance in the atherosclerosis data. Previously we have shown that the extent of iliac artery atherosclerosis is essentially the same in the left and right arteries ($r=0.97$), and that it is highly correlated with coronary artery plaque extent ($r=0.86$) (55). In the current study, pretreatment iliac artery atherosclerosis was also significantly correlated with mean CAA at necropsy ($r=0.49$, $p=0.001$). Thus, iliac artery atherosclerosis extent was used as a covariate to adjust for pretreatment individual differences in atherosclerosis extent. CAA was analyzed using a 2 (nondepressed, depressed) $\times$ 2 (placebo, sertraline) $\times$ 5 (artery blocks) mixed models analysis of covariance (ANCOVA). Anxious and depressive behavior was analyzed using a 2 (pretreatment, treatment phase) $\times$ 2 (placebo, sertraline group) mixed models ANOVA. The remaining pathophysiology measurements were analyzed by a 2 (nondepressed, depressed) $\times$ 2 (placebo, sertraline) ANOVA. All tests were 2-sided and the level of significance was set at $p=0.05$. All data are expressed as means $\pm$ SEMs.

Results

Pretreatment Characteristics

Means, SEMs and statistics for Pretreatment variables are depicted in Table 1. The placebo and sertraline groups were well matched on depressive behavior, BW, BMI, TPC, HDLC, mean peak luteal phase progesterone concentrations, number of menstrual cycles, and average cycle length. As previously observed, depressed monkeys had significantly lower BW, BMI, and HDLC, and higher average 24 hour HRs than their nondepressed counterparts (42,43). They also had longer menstrual cycles, on average, but this effect did not reach significance ($p=0.060$). Pretreatment iliac artery atherosclerosis extent was variable. On average, the depressed monkeys had more extensive atherosclerosis than nondepressed monkeys in the sertraline treatment group, and the opposite pattern was observed in the placebo group; however this interaction effect did not reach significance.

Treatment Phase Characteristics

Means, SEMs and statistics for physiological variables are depicted in Table 2. Placebo and sertraline treated groups were not different in BW, BMI, TPC, HDLC, mean peak luteal phase progesterone concentrations, and the number of menstrual cycles in a 12 month period, as was observed prior to treatment. During the treatment phase, depressed monkeys had significantly lower BW, BMI and HDLC, and longer menstrual cycles than their

nondepressed counterparts. While 24 hour HRs were higher on average in the depressed monkeys, this effect was no longer significant.

Behavioral Effects of Sertraline (Figure 2)

Sertraline had no effect on depressive behavior (Figure 2A, phase $\times$ treatment interaction $F[1, 40]=0.64$, $p=0.43$) but significantly reduced behavioral indicators of anxiety (Figure 2B, phase $\times$ treatment interaction $F[1, 40]=0.440$, $p=0.041$).

Coronary Artery Atherosclerosis

Figure 3 depicts coronary artery atherosclerosis extent expressed as raw means and SEMs in each block of the left anterior descending, the left circumflex and the right coronary arteries grouped by depressed versus nondepressed (3A) and sertraline versus placebo (3B). Average plaque areas were greater in all five blocks of all three coronary arteries in depressed compared to nondepressed monkeys. Likewise, average plaque areas were greater in all five blocks of all three coronary arteries in sertraline compared to placebo treated monkeys. These data were analyzed by a 2 (Depressed, Nondepressed) $\times$ 2 (Placebo, Sertraline) $\times$ 3 arteries (LAD, LCX, RCA) ANCOVA (averaged across blocks within each artery) adjusted for pretreatment iliac artery atherosclerosis extent. The adjusted means of the distributions of transformed data, converted to original units, from this analysis are shown in Figure 4. These represent the best estimate of the magnitude of the observed differences between sertraline and placebo treatment groups, and between depressed and nondepressed animals.

Figure 4A depicts the mean plaque area in each of the three coronary arteries. Significant main effects of depression, sertraline treatment, and artery were observed, however, no interaction effects reached significance. Plaque size was greatest in the LCX and least in the RCA ($F[1,37]=6.48$, $p=0.003$). Figure 4B depicts the main effect of depression and Figure 4C depicts the main effect of sertraline, averaged over the three coronary arteries. Depressed monkeys had more atherosclerosis than nondepressed monkeys (Figure 4B, $F[1,37]=4.69$, $p=0.037$). Monkeys treated with sertraline had more extensive atherosclerosis than those in the placebo group (Figure 4C, $F[1,37]=4.32$, $p=0.044$). Although the interaction effect did not reach significance ($F[1,37]=1.06$, $p=0.31$), the additive effects of sertraline and depression resulted in CAA extent in sertraline-treated depressed monkeys that was 4.9 times greater than that observed in untreated depressed monkeys, and 6.5 times greater than that observed in nondepressed monkeys (Figure 4D).

Discussion

This is the first published study examining the effects of long term SSRI treatment on CAA in a placebo-controlled randomized preclinical trial. The results suggest that sertraline may exacerbate atherosclerosis in the coronary arteries. This finding is consistent with the observations of Reickmann et al of increased cardiovascular morbidity and mortality in patients using SSRIs (37). No deleterious effects of sertraline on CHD risk factors including measures of obesity and lipid metabolism were observed suggesting that SSRI effects on lipid metabolism and obesity measures observed in clinical studies may be due to the disease

for which the SSRIs are being prescribed rather than a drug effect, *per se*. The observation that CAA is exacerbated in depressed monkeys replicates previous observations (43).

An important strength of the trial was the use of stratified randomization to balance treatment groups controlling for pretreatment differences in atherosclerosis extent and rates of depressive behavior. The ability to estimate individual differences in atherosclerosis prior to treatment, balance the treatment groups on pretreatment atherosclerosis extent, and co-vary pretreatment atherosclerosis assures that observed treatment effects were likely due to treatment and not to pretreatment differences in the groups. This design provided the opportunity for analysis of sertraline treatment effects on atherogenesis independent of the effects of depression, eliminating an important confound characteristic of clinical studies. The significant main effect of sertraline without a significant interaction means that SSRI treatment exacerbates CAA independent of depression; sertraline exacerbated CAA in depressed and nondepressed individuals. Furthermore, since sertraline and other SSRIs are widely prescribed for disorders other than depression, the effects of sertraline on nondepressed individuals is as important as the effects on depressed individuals.

Another key feature of this study was the use of subjects that were naïve to antidepressant treatment prior to the onset of the study. A number of other characteristics of the study that might affect atherosclerosis progression were also tightly controlled including sex, diet, other drug exposures, light/day cycles, housing, and treatment compliance. Plasma concentrations of sertraline and desmethylsertraline demonstrated that the drug was successfully delivered via oral dosing and resulted in blood levels similar to those in patients (45). CSF monoamine metabolite concentrations evidenced effects on the central nervous system similar to those observed in human beings (46).

Another strength of this preclinical trial was the use of a well-established NHP model of depression. Monkeys that display depressive behavior share many central and peripheral characteristics of depression with depressed human beings. Perhaps the most important shared primate trait, for the purposes of this study, is the susceptibility of depressed monkeys to develop significantly more extensive CAA than their nondepressed counterparts (43 and this report). While comorbidities are common in human health, animal models of comorbidities are rare. The use of this primate model allows a placebo-controlled long term randomized trial design in a model closely related to human beings, facilitating basic to clinical translation.

As in a previous study (43), depressed monkeys had lower BW, BMI, and HDLC, higher 24 hour HR, and some evidenced of ovarian impairment at the outset of the treatment period. The differences between depressed and nondepressed monkeys persisted through the treatment phase except for the HR differences. These remained elevated in depressed animals but HRs overall were higher and more variable in the treatment phase, and the depression difference fell below the level of statistical significance.

The results of this preclinical trial suggest that sertraline increases atherogenesis, and the effect was particularly marked in depressed monkeys. Sertraline did not significantly alter lipids or BMI under experimental conditions in which all subjects were consuming the same

diet, or any other risk factors reported here. In addition, transthoracic doppler echocardiography was performed in these animals prior to necropsy and the results were previously reported (57). Behavioral depression was accompanied by some differences in cardiac function, although not in ways classically associated with subclinical heart failure. Sertraline may have mildly improved left ventricular filling. Importantly, no deleterious effects of sertraline on heart function were observed (57). Since none of the traditional cardiovascular risk factors examined were worsened by sertraline, the mechanism of this effect remains to be elucidated. However, sertraline has multiple effects which could influence events in the artery wall. For example, sertraline is a potent vasodilator (58,59) and interferes with platelet function (60,61), although how these might adversely influence atherosclerosis is unclear. More research is needed to understand the effects of SSRIs on artery wall biology.

Sertraline did not decrease depressive behavior, although it did significantly decrease behavioral indices of anxiety. The efficacy of sertraline, and other SSRIs, for depression has been reassessed in recent years principally due to strong publication bias (62,63). However, sertraline is widely prescribed and has been shown to be efficacious for the treatment of anxiety disorders in people (64,65). Displacement behaviors such as self-grooming, touching or scratching were proposed several years ago by Maestripierei (47) as a measure of anxiety based in part on observations of similar behaviors in patients diagnosed with anxiety (48,49). In group-living adult female cynomolgus macaques, the acute administration of the anxiolytic lorazepam selectively reduces the frequency of scratching (50), and may have similar effects on self-grooming (47). Thus, the neurobiological substrates of these behavioral indices of anxiety in monkeys appear to be similar to those of human anxiety. We have also observed shorter term (6 weeks) influences of sertraline on social behavior including decreased aggression and increased affiliation (44) corroborating a lower arousal state in monkeys treated with sertraline versus placebo.

This study focused on atherosclerosis development during the late premenopausal years in which there is a high rate of SSRI use by women. Atherosclerosis extent at this age sets the stage for postmenopausal CHD risk. While the results of this nonhuman primate study are compelling, replication, and the elucidation of mechanisms of action are needed to understand risk levels in patients, and the generalizability of the findings across gender, age and ethnicity needs to be assessed. However, these data suggest that a conservative approach to prescribing SSRIs for a broad range of disorders or for long time periods may be warranted, and that further study is critical given the widespread use of these medications.

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Acronyms

CHD	coronary heart disease
SSRI	selective serotonin reuptake inhibitor

CAA	coronary artery atherosclerosis
BW	body weight
BMI	body mass index
HPA	hypothalamic-pituitary-adrenal
HDL	high-density lipoprotein cholesterol
TPC	total plasma cholesterol
SADHART	Sertraline AntiDepressant Heart Attack Trial
ENRICH	ENhancing Recovery in Coronary Heart Disease
HCl	hydrochloride
CSF	cerebrospinal fluid
HR	heart rate
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
RCA	right coronary artery
ANCOVA	analysis of covariance
ANOVA	analysis of variance
SEM	standard error of the mean

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Experimental Design

Figure 1.

A. Experimental Design 42 adult female monkeys consumed a Western diet for an 18 month Pretreatment Phase, during which behavior and physiology was assessed. At the end of the Pretreatment Phase the iliac biopsy was biopsied and atherosclerosis extent measured. The monkeys were assigned to the Sertraline or Placebo Treatment groups balanced on Pretreatment rates of depression, body weight, and iliac artery atherosclerosis extent. The monkeys continued to consume a Western diet during the 18 month Treatment Phase, during which behavior and physiology was assessed. The animals were then necropsied, and coronary artery atherosclerosis was measured. **B. Depressed (left) and Alert (right) Monkey.** The definition of depressive behavior includes three components: 1) exhibition of a slumped or collapsed body posture; 2) a relative lack of responsiveness to environmental stimuli to which other monkeys are attending; and 3) open eyes to distinguish this behavior from resting (41,42).

Figure 2.
The Effects of Sertraline Treatment on Behavioral Indicators of A: Depression, and B: Anxiety. Anxious and depressive behavior was analyzed using a 2 (Pretreatment, Treatment) $\times$ 2 (Placebo, Sertraline) mixed models ANOVA. Sertraline had no effect on depressive behavior (phase $\times$ treatment interaction $p=0.43$), but reduced behavioral indicators of anxiety (phase $\times$ treatment interaction $p=0.041$).

Figure 3.
Coronary Artery Atherosclerosis extent expressed as raw means and SEMs in each block of the left anterior descending, the left circumflex and the right coronary arteries grouped by: **A.** Depressed versus Nondepressed; and **B.** Sertraline versus Placebo.

Figure 4. The Effects of Sertraline on Atherosclerosis in Depressed and Nondepressed Macaques
 The data were analyzed by a 2 (Depressed, Nondepressed) $\times$ 2 (Placebo, Sertraline) $\times$ 3 Coronary Arteries (LAD, LCX, RCA) ANCOVA adjusted for pretreatment iliac artery atherosclerosis extent: **A.** Atherosclerosis extent in the Left Anterior Descending (LAD), Left Circumflex (LCX), and Right Coronary Artery (RCA). Main effects of depression, treatment, and artery ($p=0.003$) on plaque area were observed; **B.** Main effect of depression on mean coronary artery plaque area, $p=0.036$; **C.** Main effect of sertraline treatment on mean coronary artery plaque area, $p=0.044$; **D.** Mean coronary artery plaque area in depressed and nondepressed monkeys in the placebo and sertraline treated groups. Adjusted means of the distributions of transformed data converted to original units are depicted in all graphs.

Table 1

Pretreatment Characteristics of the Study Population

Variables	Placebo		Sertraline		Effects		
	Non Dep n=12	Dep n=9	Non Dep n=11	Dep n=10	Depression p=	Sertraline p=	Depression × Sertraline p=
Depressive Behavior freq/hr	0.01 (0.49)	2.10 (0.56)	0.01 (0.51)	1.37 (0.53)	0.002	0.48	0.49
BW kg	3.93 (0.21)	2.77 (0.24)	4.01 (0.22)	3.11 (0.23)	<0.001	0.35	0.56
BMI kg/m ²	51.7 (2.0)	39.5 (2.3)	44.8 (2.1)	39.7 (2.2)	<0.001	0.13	0.11
TPC mg/dl	315 (26.0)	345 (30.1)	321 (27.2)	348 (28.5)	0.32	0.87	0.94
HDLc mg/dl	61.3 (5.1)	48.1 (5.9)	64.4 (5.3)	52.0 (5.6)	0.030	0.53	0.94
TPC:HDLc	6.20 (1.0)	7.81 (1.1)	6.04 (1.0)	7.43 (1.1)	0.16	0.80	0.92
Mean Peak Luteal Phase Progesterone	11.4 (1.3)	10.2 (1.5)	10.1 (1.4)	11.8 (1.4)	0.86	0.95	0.33
Number of Cycles	10.2 (0.34)	9.3 (0.39)	9.5 (0.35)	9.5 (0.37)	0.24	0.39	0.19
Cycle Length days	28.9 (1.2)	32.8 (1.4)	29.4 (1.3)	30.7 (1.3)	0.060	0.53	0.32
Mean 24 hour Heart Rate bpm	139 (4.7)	148 (5.5)	131 (4.9)	149 (5.2)	0.010	0.53	0.45
Age years	17.3 (0.54)	16.2 (0.62)	17.9 (0.56)	17.5 (0.59)	0.20	0.12	0.55
Iliac Artery Atherosclerosis mm ²	0.16 (0.04)	0.06 (0.05)	0.03 (0.04)	0.10 (0.05)	0.78	0.37	0.06

BW=body weight, BMI=body mass index, TPC=total plasma cholesterol, HDLC=high density lipoprotein cholesterol, Nondep=monkeys exhibiting little or no depressive behavior, Dep=monkeys exhibiting depressive behavior

Table 2

Characteristics of the Study Population during the Treatment Phase

Variables	Placebo		Sertraline		Effects		
	Non Dep n=12	Dep n=9	Non Dep n=11	Dep n=10	Depression p=	Sertraline p=	Depression × Sertraline p=
Depressive behavior freq/hr	0.55 (0.91)	4.50 (1.05)	0.08 (0.95)	5.85 (1.00)	p< 0.001	0.70	0.39
BW kg	4.24 (0.24)	2.86 (0.27)	3.96 (0.25)	3.04 (0.26)	p< 0.001	0.84	0.39
BMI kg/m ²	53.7 (2.3)	40.3 (2.7)	45.2 (2.4)	39.6 (2.5)	p< 0.001	0.07	0.12
TPC mg/dl	305 (19)	322 (23)	321 (20)	324 (21)	0.65	0.65	0.75
HDL C mg/dl	58.3 (5.0)	45.5 (5.7)	66.5 (5.2)	51.6 (5.4)	0.010	0.19	0.84
TPC:HDL C	5.93 (0.73)	7.39 (0.85)	5.77 (0.77)	6.75 (0.80)	0.13	0.62	0.77
Mean Peak Luteal Phase Progesterone	12.1 (1.0)	9.5 (1.1)	11.3 (1.0)	11.6 (1.1)	0.30	0.53	0.17
No. of Cycles	12.5 (0.29)	11.4 (0.34)	12.0 (0.31)	12.0 (0.32)	0.10	0.93	0.10
Cycle Length days	28.4 (0.80)	31.8 (0.93)	29.6 (0.84)	30.2 (0.88)	0.030	0.79	0.11
Mean 24 hr Heart Rate bpm	150 (5.6)	154 (6.5)	143 (5.9)	156 (6.2)	0.17	0.68	0.42

BW=body weight, BMI=body mass index, TPC=total plasma cholesterol, HDLC=high density lipoprotein cholesterol, Nondep=monkeys exhibiting little or no depressive behavior, Dep=monkeys exhibiting depressive behavior